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Circulation. Author manuscript; available in PMC 2015 October 08.

Published in final edited form as:
Circulation. 2014 January 21; 129(3): 281–284. doi:10.1161/CIRCULATIONAHA.113.006941.

Breastfeeding and Cardiometabolic Profile in Childhood:

How Infant Feeding, Preterm Birth, Socioeconomic Status, and Obesity May Fit Into the Puzzle

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Keywords

Editorials; breastfeeding; cardiovascular disease; obesity

Although the observed association between breastfeeding and cardiometabolic profile in childhood and adolescence in previous studies has biological plausibility, the precise mechanism and magnitude remain far from being fully understood.[1] Early nutrition and epigenetic programming,[2] anti-inflammatory properties,[3] and cardiorespiratory fitness[4] are among numerous hypotheses that are currently being actively investigated.

In this issue of *Circulation*, Martin et al[5] report on this subject. Their intervention study began in 1996 to 1997 in 31 Belarussian maternity hospitals and affiliated outpatient clinics with an enrollment of 17046 breastfeeding mothers of healthy term infants. The trial was originally designed to assess the effects of a breastfeeding promotion and support intervention on duration of breastfeeding. Duration of both exclusive (infant only receives breast milk without any additional food or drink, not even water) and any breastfeeding (includes nonexclusive and exclusive) was assessed in the intervention and nonintervention groups.[6] The planned 11.5-year follow-up of ≈80% of study participants who had fasted for the follow-up assessment and did not have diabetes mellitus allowed the authors to test whether an intervention to improve breastfeeding duration and exclusivity also influenced cardiometabolic risk factors in childhood. No significant differences between the intervention and control groups were found in levels of blood pressure, fasting insulin, adiponectin, glucose, apolipoprotein A1, or metabolic syndrome.

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosures
None.

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Original Study Design and Assumptions Applied in the Follow-Up Analysis

The results of the study by Martin et al[5] should be interpreted with several considerations taken into account. First, all women enrolled in the trial expressed an intention to breastfeed on admission to the postpartum ward, and they initiated breastfeeding. The intervention successfully increased the proportion of women who were exclusively breastfeeding at 3 months (43.3% versus 6.4%) and 6 months (7.9% versus 0.6%) postpartum. Although a significantly larger proportion of infants in the intervention group were breastfed during the first year of life (49.8% and 19.7% at 6 and 12 months of age, respectively), 36.1% and 11.4% of infants from the no-intervention group were also breastfed at 6 and 12 months of age. Thus, the results of this study in which longer durations of breastfeeding were compared with shorter durations of breastfeeding cannot be equated to results from studies comparing breastfeeding to formula feeding.

In addition, the conclusions in this study are based on the implicit assumption that the characteristics of 2 groups of participants formed a decade ago remain the same. Many events may have occurred in each participant in the trial that may have changed the comparability of randomized groups. For instance, diet and physical activity are important determinants of cardiovascular risk profile in childhood and adolescence. Although the authors noted that it is unlikely that the intervention group had a poorer diet than the control group, the authors cannot rule out the possibility that changes in sociodemographic and environmental factors took place during the study follow-up period.

Is It Breastfeeding or Variations in Study Populations?

Even in studies comparing breastfed infants with formulafed infants, the effects of breastfeeding on measurements of cardiovascular disease risk profile are usually small, and their clinical significance remains unclear. Thus, given the study design, even smaller differences are expected in the trial reported here. Indeed, in systematic reviews and meta-analyses of observational studies comparing breastfed to formula-fed infants, the effect of breastfeeding on systolic blood pressure was very moderate (1.1 mm Hg).[7] Another point to consider is that only full-term singleton infants weighing ≥2500 g and their healthy mothers were enrolled in the intervention study. It has been shown that the beneficial effects of breast milk on cardiovascular disease risk factors may be larger and thus more likely to be detectable in preterm infants. For instance, in a cohort of preterm children in 2 parallel randomized trials in 5 neonatal units in the United Kingdom, mean arterial blood pressure at age 13 to 16 years was 6.5 mm Hg lower in the 66 children fed breast milk obtained from a human milk bank (alone or in addition to mother's own milk) than in the 64 children fed preterm formula.[8] The authors of the UK preterm trial also reported lower levels of C-reactive protein and low-density lipoprotein to high-density lipoprotein cholesterol ratio in adolescents who had been randomized to receive banked breast milk than in those given preterm formula.[9] Finally, Belarus has a well-structured healthcare system, but the annual gross domestic product per capita was <$7000 US during >10 years of the study follow-up period.[10] Evidence that is available primarily from observational studies in other populations has shown that children and adults who were breastfed have lower levels of total blood cholesterol, lower risk of type 2 diabetes mellitus, and marginally lower levels of adiposity

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and blood pressure than those who were formula fed.[7] However, no evidence that longer duration of breastfeeding is protective against adult hypertension, diabetes mellitus, or overweight/adiposity was found in studies limited to low-/middle-income populations.[11] In contrast, the later introduction of complementary foods demonstrated protective effects against adult adiposity, a known correlate of cardiometabolic risk. Body mass index (BMI) and waist circumference decreased significantly, by 0.19 kg/m^2 and 0.45 cm, respectively, per each 3-month increase in age at introduction of complementary foods. Unfortunately, no information on age of introduction and type of complementary foods was provided in the report by Martin et al.[5]

Addressing the Growing Obesity Epidemic Is Likely to Be a Major Factor in Improving the Cardiometabolic Profiles of US Children and Adolescents

In the study population at 11.5 years of age, the prevalence of obesity (defined as BMI values at or above the 95th percentile of the Centers for Disease Control and Prevention sex-specific BMI growth charts)[12] was ≈5.0% (5.4% and 4.7% for the intervention and control group, respectively),[13] which is ≈3.5 times lower than the prevalence of obesity among US children aged 6 to 11 years reported in 2009 to 2010.[14] The prevalence of obesity in the US children and adolescents aged 2 to 19 years has increased dramatically from 5.0% in the early 1970s to 16.9% in 2009 to 2010.[14, 15] According to the most recent report from the Centers for Disease Control and Prevention, although the rate of childhood obesity leveled off during 1999 to 2010 among girls, it continues to increase among boys.[14] Currently, numerous studies performed among children and adolescents have confirmed that the same cardiovascular risk factors associated with obesity, such as type 2 diabetes mellitus, hypertension, and abnormal lipid profile, have substantially higher prevalence in obese children than in normal-weight children.[16] Consistent adverse associations between obesity and cardiovascular disease risk factors were reported in a systematic review and meta-analysis of 63 studies of almost 50 000 children aged 5 to 15 years.[16] In obese children compared with normal-weight children, systolic blood pressure was higher by 7.49 mm Hg. An increase of 1.0 mg/dL in total cholesterol and 1.4 mg/dL in low-density lipoprotein cholesterol for each BMI point increase was reported in these analyses. Obesity also adversely affected concentrations of fasting insulin, insulin resistance, and size of left ventricle. The PROBIT (Promotion of Breastfeeding Intervention Trial) researchers reported no difference in the prevalence of obesity between the intervention and control groups.[13] This may be another reason why no differences in cardiometabolic profiles were found between the intervention and control groups in the study by Martin et al.[5]

What Is the Current Evidence on Effectiveness of Weight-Related Interventions to Improve Cardiometabolic Profiles of Children and Adolescence?

Reducing the risk of obesity is one of the most plausible mechanisms underlying the positive effects of breastfeeding on cardiometabolic profile in children. Several meta-analyses of observational studies examined the antiobesogenic effects of breastfeeding.[17, 18] The results of 2 of these analyses showed a 4% reduction in overweight for each month of breastfeeding

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and a 15% decrease in the risk of obesity for exclusive breastfeeding compared with formula feeding in later life. However, the reported magnitude of associations in the studies included in the reviews was modest and varied among the studies, possibly because of factors that were not taken into account in the studies.

It is speculative to predict what the strength and direction of associations between breastfeeding and cardiometabolic profile would be if the study were to take place in the United States. Nevertheless, interventions limited to promotion of breastfeeding are unlikely to have a significant impact on the cardiometabolic profile of children and adolescence given the high prevalence of childhood obesity in the United States. Most of the currently available studies that have examined the effectiveness of interventions to reduce cardiometabolic risks in the pediatric population have been weight-related studies. In a systematic review and meta-analysis of 8 randomized trials among obese children 6 to 12 years of age, educational interventions with follow-up ≥6 months resulted in a significant reduction in waist circumference (by 3.2 cm in 3 studies) and BMI (by 0.9 kg/m^2 in 5 studies) compared with usual care or no intervention.[19] Interventions in these studies were performed in school or family settings or both, through “classroom lessons to increase the intake of fruits and vegetables and/or physical activity, modification of physical education classes and/or family-based programs (counseling, training, orientations or group or individual meetings).”[19] The effect of intervention on blood pressure among these studies was assessed in only 2 studies, with significant 3.7-mm Hg reductions observed for diastolic blood pressure in 1 study. However, in that review, no differences in outcomes were found in 18 studies that investigated the effectiveness of obesity prevention interventions. In another systematic review[20] of 15 randomized, controlled trials among overweight and obese children aged ≤18 years, the addition of exercise to dietary intervention compared with the diet-only intervention resulted in significantly larger improvements in levels of high-density lipoprotein cholesterol (3.9 mg/dL), fasting glucose (2.2 mg/dL), and fasting insulin (−2.8 μIU/mL) at 6-month follow-up.

Parental involvement appears to play an important role in child weight-reduction interventions. The results of 36 randomized, controlled studies showed that child and adolescent participants in weight-related interventions that required parental participation achieved BMIs ≈1.2 kg/cm2 less than the respective control group’s participants.[21] In addition, in that analysis, compared with shorter interventions with parental participation, longer interventions with parental participation appeared to be more successful. Only 8 of these 36 studies examined the effects of weight reduction on cardiometabolic indicators. Significantly larger improvements in systolic blood pressure (4 studies), fasting insulin (1 study), C-reactive protein (1study), and lipid levels (3 studies) were reported in the groups with parental involvement.

Multiple studies demonstrated the effectiveness of school-based interventions focused on weight loss or healthy weight maintenance, improved diet, or increased physical activity.[22] However, only 12 of them examined the effects of these interventions on the cardiometabolic profile in children. The results of a systematic review of school-based interventions[22] aimed at reducing BMI or weight in children ≤18 years of age showed that interventions targeted at overweight/obese children reduced their BMI by 0.35 kg/m2,

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whereas those delivered to all children reduced BMI by 0.16 kg/m2. Physical activity used in isolation (11 studies) or combined with improved nutrition (29 studies) reduced BMI by 0.13 and 0.17 kg/m2, respectively.[22] In 12 of 41 studies that reported cardiometabolic measurements, children in the intervention group had a significantly larger decrease in blood pressure (7 studies), lipids (including total cholesterol, low-density lipoprotein cholesterol, or triglyceride; 6 studies), fasting insulin (1 study), or fasting glucose levels (1 study). In a systematic review of 44 studies,[23] school-based physical activity interventions were effective in increasing the duration of physical activity by 5 to 45 minutes per day, reducing time spent watching television by 5 to 60 minutes per day, and increasing the physical fitness level of an individual; however, the effects of physical activity on blood pressure and BMI in that review were inconsistent across studies, and the strength and direction of associations were dependent on type of intervention and study duration. Only 4 and 3 of the 16 studies demonstrated statistically significant decreasing effects on mean systolic and diastolic blood pressure, respectively. Significant changes in BMI were reported in some of these significant association studies (1 of 4 and 2 of 3 of the systolic and diastolic blood pressure studies, respectively). Given that physical activity seldom alters total cholesterol and low-density lipoprotein cholesterol unless it is accompanied by a reduction in dietary fat intake and body weight loss in adults,[23] it is not surprising that only 1 of the 10 studies reported a statistically significant positive effect on mean blood cholesterol level.[24]

Conclusions

The present study by Martin et al[5] is a unique and valuable contribution to a better understanding of the cardiometabolic effects of breastfeeding in childhood and adolescence. The absence of significant differences in cardiometabolic profiles between the intervention and control groups does not call into question the importance of promoting breastfeeding, because breastfeeding has many other benefits for infant health. Unfortunately, today, virtually every specialty of medical practice is already facing, or will be facing in the near future, the adverse cardiometabolic consequences of the childhood obesity epidemic. It is hard to imagine improving the cardiovascular health of US children and adolescents without recognizing the urgency of addressing the childhood obesity problem. This challenging goal cannot be achieved without identifying interventions supported by rigorous evidence from studies with sophisticated design, adequate sample size, and sufficient duration of follow-up.

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